REMARKS/ARGUMENTS

Claims 11 and 14-25 are pending.

Claims 26-39 were withdrawn based on the Office's imposed Restriction requirement and therefore cancelled.

Support for the amendment to claim 23 is found on pages 53-56.

Claim 11 is amended to define the disorder specifically as type II diabetes (Diabetes II) as previously presented in claim 13, now cancelled.

No new matter is added by the submission of amended claims.

Claim 23 is rejected under 35 U.S.C. 112 ¶1 for lack of written description and is believed to be no longer applicable as the drugs identified as an aldose reductase inhibitor, an alpha-glucose inhibitor, a sulfonyl urea agent, a biguanide, a thiazolidine, a PPARs agonist, and GSK-3 inhibitor are identified based on what is described in the application at pages 53-56.

Thus, the specification provides a sufficient description of a the supplemental drugs listed in claim 23. Applicants request that the rejection be withdrawn.

The rejections based on Arkinstall have been maintained. It is requested that the rejections be withdrawn as Arkinstall, by itself or combined with the other cited publications neither describes or suggests, explicitly or inherently, the treatment of type II diabetes with the sulfonamide compounds of formula (I) as presented here.

The legal requirement for inherency is that "each and every time" the drug is administered in the prior art (in autoimmune patients) the administration must also treat what we claim here (diabetes type II). Autoimmune diseases relate to a vast spectrum of disorders

involving the thyroid, lupus, multiple sclerosis, rheumatoid arthritis and others. (see the attached listing as an example). Type-II diabetes is not known to be an autoimmune disease. Thus, when an administering compound as taught by Arkinstall, one would not necessarily, each and every time, also treat Type-II diabetes as claimed.

As has been previously discussed, Arkinstall describes generic compounds broadly encompassing the sulfonamide compounds claimed. Arkinstall discloses that the JNK signaling pathway is implicated in cell proliferation and could play an important role in autoimmune diseases [0010]. Arkinstall shows that the disclosed generic compounds modulate the JNK pathway as JNK inhibitors, notably JNK2 and JNK3, and are useful for the treatment of the immune and neuronal system disorders [0107], [0135]-[0140]. Arkinstall does not teach selecting specific (e.g., claimed in this application) sulfonamide derivatives and using the selected derivatives for treating other JNK mediated disorders, i.e., a metabolic disorder mediated by insulin resistance or hyperglycemia.

Although Bennett discloses that one JNK inhibitor (CC105 small molecule) has potential in treating insulin resistance and obesity, it does not mean that all Arkinstall compounds of general formula I are necessarily effective for treating diabetes II.

Bozyczko-Coyne, Curr. Drug Target – CNS & Neurol. Disorders, 1:31-49, 42-43 (2002), shows that the JNK pathway is very complex, involves many levels of regulations, genes, proteins, and disorders. The JNK pathway is implicated in a large number of physiological and pathological functions. See Bozyczko-Coyne, at 43-43. Moreover, the complexity of the organization and regulation at all levels within the JNK signaling cascade continues to evolve. Further, because of the complex cross talk within this signaling cascade as well as its cell type and response specific modulation, it is difficult to predict potential adverse events that might

arise from pathway inhibition (Bozyczko-Coyne, page 43). Owing to the breadth of physiological functions mediated via signaling through the JNK family, direct inhibition at the level of the JNK could prove to have liabilities (Bozyczko-Coyne, page 31. right col.).

Therefore, Bennett at best suggests to try the JNK inhibitors for treatment diabetic disorder (one of many disorders modulated via the JNK pathway), but does not support the conclusion that all Arkinstall compounds do treat a type II diabetes.

The Arkinstall compounds display inhibitory activity of the JNK pathway. However, Arkinstall only describes using the compounds for treating disorders of the autoimmune and neuronal system, see [0001], [0017], and [0135]-[0140]. Arkinstall does not enable treating all disorder related to the inhibition of the JNK pathway. Arkinstall does not provide sufficient nexus between autoimmune and neuronal disorders and type II diabetes so that they are substantially related and can be treated with the same compounds.

In contrast, this specification describes using the claimed compounds in *in vivo* assay in db/db mice to determine anti-diabetic effect of the test compounds in a model of postprandial glycemia (page 60-61). The experiment on pages 60-61 shows that the blood glucose level and blood insulin were decreased in the treated animals compared to the untreated animals.

The obviousness rejection combining Sterne and Weber with Arkinstall is largely to allege that the supplemental drugs were known and therefore obvious to use with Arkinstall. Although Applicants respectfully disagree with the supposition of the rejection for the sake of brevity it is again stressed that as Arkinstall neither explicitly or inherently describe the treatment of type II diabetes as claimed, the obviousness rejection based on the combination of citations is inapplicable to the claims.

Applicants request that the rejections based on Arkinstall be withdrawn.

A similar argument as discussed applies to the obviousness type-double patenting rejections that have been maintained. However, as the rejections are provisional in nature, it is requested that the rejections be held in abeyance since the alleged conflicting claims have not yet been patented. Further, Applicants note the following from MPEP § 822.01:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

A Notice of Allowance for all pending claims is requested.

Respectfully submitted,

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List of autoimmune diseases

From Wikipedia, the free encyclopedia

Autoimmune diseases arise from an overactive immune response of the body against substances and tissues normally present in the body. In other words, the body attacks its own cells. Autoimmune diseases are a major cause of immune-mediated diseases.

Today there are more than 40 human diseases classified as either definite or probable autoimmune diseases, and they affect 5% to 7% of the population. Almost all autoimmune diseases appear without warning or apparent cause, and most patients suffer from fatigue.

Contents

Causes

The causes of autoimmune diseases are still relatively unknown. We do know that autoimmune diseases are not contagious, nor are they caused by behavior.

Gender influence

Women tend to be affected more often by autoimmune disorders; nearly 79% of autoimmune disease patients in the USA are women. Also they tend to appear during or shortly after puberty. It is not known why this is the case, although hormone levels have been shown to affect the severity of some autoimmune diseases such as multiple sclerosis.[1] Other causes may include the presence of fetal cells in the maternal bloodstream. [2]

Autoimmune diseases

Diseases with a complete or partial autoimmune etiology:

Accepted

The "Mesh" column lists those conditions that are classified as autoimmune by the MeSH system.

Name	MeSH?	ICD-10	Description

Acute disseminated encephalomyelitis (ADEM)	yes	G04.0	is a form of encephalitis caused by an autoimmune reaction and typically occurring a few days or weeks after a viral infection or a vaccination.
Addison's disease	yes	E27	is often caused by autoimmune destruction of the adrenal cortex.
Ankylosing spondylitis	yes	M08.1, M45.	is a chronic, painful, progressive inflammatory arthritis primarily affecting spine and sacroiliac joints, causing eventual fusion of the spine.
Antiphospholipid antibody syndrome (APS)	yes	D68.8	affects the blood-clotting process. It causes blood clots to form in veins and/or arteries.
Aplastic anemia	no	D60	is often caused by an autoimmune attack on the bone marrow.
Autoimmune hepatitis	no	K75.9	is a disorder wherein the liver is the target of the body's own immune system.
Autoimmune Oophoritis	no	N70	is a disorder in which the immune system attacks the female reproductive organs.
Celiac disease	no	K90.0	is a disease characterized by chronic inflammation of the proximal portion of the small intestine caused by exposure to certain dietary gluten proteins.
Crohn's disease	no	K50	is a form of inflammatory bowel disease characterized by chronic inflammation of the intestinal tract. Major symptoms include abdominal pain and diarrhea. There is also a theory that Crohn's Disease is an infectious disease caused by Mycobacterium avium paratuberculosis.
Diabetes mellitus type 1	yes	E10	when it is characterized by a deficiency or absence of insulin production (Type I), is often the consequence of an autoimmune attack on the insulin-producing beta cells in the islets of Langerhans of the pancreas.
Gestational pemphigoid	no	O26.4	is a pregnancy-related blistering condition where autoantibodies are directed against the skin.
Goodpasture's syndrome	yes	M31.0	is a disease characterised by rapid destruction of the kidneys and haemorrhaging of the lungs through autoimmune reaction against an antigen found in both organs.
Graves' disease	yes	E05.0	is the most common form of hyperthyroidism, and is caused by anti-thyroid antibodies that have the effect of stimulating (agonist) the thyroid into overproduction of thyroid hormone.
Guillain-Barré syndrome (GBS)	yes	G61.0	is an acquired immune-mediated inflammatory disorder of the peripheral nervous system (i.e., *not* the brain and spinal column). It is also called acute inflammatory demyelinating polyneuropathy, acute idiopathic

			polyradiculoneuritis, acute idiopathic polyneuritis and Landry's ascending paralysis.
Hashimoto's disease	yes	E06.3	is a common form of hypothyroidism, characterised by initial inflammation of the thyroid, and, later, dysfunction and goiter. There are several characteristic antibodies (e.g., anti-thyroglobulin).
Idiopathic thrombocytopenic purpura	yes	D69.3	is an autoimmune disease where the body produces anti-platelet antibodies resulting in a low platelet count
Kawasaki's Disease	no	M30.3	is often caused by an autoimmune attack on the arteries around the heart.
Lupus erythematosus	yes	L93, M32	is a chronic (long-lasting) autoimmune disease wherein the immune system, for unknown reasons, becomes hyperactive and attacks normal tissue. This attack results in inflammation and brings about symptoms. This is a "Non-organ-specific" type of autoimmune disease.
Mixed Connective Tissue Disease			has features of other connective tissues diseases — lupus, rheumatoid arthritis, scleroderma and polymyositis. The presence of a specific antibody — called U1-RNP is needed for diagnosis.
Multiple sclerosis	yes	G35	is a disorder of the central nervous system (brain and spinal cord) characterised by decreased nerve function due to myelin loss and secondary axonal damage.
Myasthenia gravis	yes	G70.0	is a disorder of neuromuscular transmission leading to fluctuating weakness and fatigue. Weakness is caused by circulating antibodies that block (antagonist) acetylcholine receptors at the neuromuscular junction.
Opsoclonus myoclonus syndrome (OMS)	n/a	n/a	is a neurological disorder that appears to the result of an autoimmune attack on the nervous system. Symptoms include opsoclonus, myoclonus, ataxia, intention tremor, dysphasia, dysarthria, mutism, hypotonia, lethargy, irritability or malaise. About half of all OMS cases occur in association with neuroblastoma.
Ord's thyroiditis	n/a	n/a	is a thyroiditis similar to Hashimoto's disease, except that the thyroid is reduced in size. In Europe, this form of thyroid inflammation is more common than Hashimoto's disease.
Pemphigus	yes	L10	is an autoimmune disorder that causes blistering and raw sores on skin and mucous membranes.
Pernicious anaemia	no	D51.0	is an autoimmune disorder characterised by anaemia due to malabsorption of vitamin B12
Polyarthritis in dogs	n/a	n/a	is an immune reaction severely affecting the joints of dogs. Although rare and of unknown cause it can render a dog immobile even at a very young age. Treatment

			includes cortisone-type drugs.
Primary biliary cirrhosis	no	K74.3	appears to be an autoimmune disease that affects the biliary epithelial cells (BECs) of the small bile duct in the liver. Although the cause is yet to be determined, most of the patients (>90%) appear to have auto-mitochondrial antibodies (AMAs) against pyruvate dehydrogenase complex (PDC), an enzyme that is found in the mitochondria.
Rheumatoid arthritis	yes	M05-M06	is an autoimmune disorder that causes the body's immune system to attack the bone joints.
Reiter's syndrome	no	M02	seems to be an autoimmune attack on various body systems in response to a bacterial infection and the body's confusion over the HLA-B27 marker
Sjögren's syndrome	yes	M35.0	is an autoimmune disorder in which immune cells attack and destroy the exocrine glands that produce tears and saliva.
Takayasu's arteritis	no	M31.4	is a disorder that results in the narrowing of the lumen of arteries.
Temporal arteritis (also known as "giant cell arteritis")	yes	M31.5	is an inflammation of blood vessels, most commonly the large and medium arteries of the head. Untreated, the disorder can lead to significant vision loss.
Warm autoimmune hemolytic anemia	n/a	D59.1	is a disorder characterized by IgM attack against red blood cells
Wegener's granulomatosis	no	M31.3	is a form of vasculitis that affects the lungs, kidneys and other organs.

Suspected

Diseases suspected or theorized to be linked to autoimmunity are:

- Alopecia universalis
- Autoimmune Inner Ear Disease is a syndrome of hearing loss or dizziness, similar to Meniere's disease, caused by antibodies or immune cells attacking the inner ear. See http://www.dizziness-and-balance.com/disorders/autoimmune/aied.html
- Behçet's disease
- Chagas' disease [3]
- Chronic fatigue syndrome
- Dysautonomia
- Endometriosis [4]

- Hidradenitis suppurativa [5]
- Interstitial cystitis [6]
- Lyme disease
- Morphea[7]
- Neuromyotonia [8]
- Narcolepsy [9]
- Psoriasis
- Sarcoidosis
- Schizophrenia. [10][11][12]
- Scleroderma
- Ulcerative colitis
- Uveitis
- Vitiligo [13][14]
- Vulvodynia

References

1. ^ A Gender Gap in Autoimmunity (http://www.sciencemag.org/feature/data/983519.shl). Retrieved on 2007-10-19.
2. ^ JAMA -- Abstract: Microchimerism: An Investigative Frontier in Autoimmunity and Transplantation, March 3, 2004, Adams and Nelson 291 (9): 1127 (http://jama.ama-assn.org/cgi/content/abstract/291/9/1127). Retrieved on 2007-10-19.
3. ^ Hyland KV, Engman DM (2006). "Further thoughts on where we stand on the autoimmunity hypothesis of Chagas disease". *Trends Parasitol.* **22** (3): 101-2; author reply 103. doi:10.1016/j.pt.2006.01.001 (http://dx.doi.org/10.1016/j.pt.2006.01.001). PMID 16446117 (http://www.ncbi.nlm.nih.gov/pubmed/16446117).
4. ^ Gleicher N, el-Roeiy A, Confino E, Friberg J (1987). "Is endometriosis an autoimmune disease?". *Obstetrics and gynecology* **70** (1): 115-22. PMID 3110710 (http://www.ncbi.nlm.nih.gov/pubmed/3110710).
5. ^ Clinical Trial: Etanercept in Hidradenitis Suppurativa (http://clinicaltrials.gov/show/NCT00329823). Retrieved on 2007-07-08.
6. ^ Kárpáti F, Dénes L, Büttner K (1975). "[Interstitial cystitis=autoimmune cyatitis? Interstitial as a participating disease in lupus erythematosus]" (in German). *Zeitschrift für Urologie und Nephrologie* **68** (9): 633-9. PMID 1227191 (http://www.ncbi.nlm.nih.gov/pubmed/1227191).
7. ^ Takehara K, Sato S (2005). "Localized scleroderma is an autoimmune disorder". *Rheumatology (Oxford, England)* **44** (3): 274-9. doi:10.1093/rheumatology/keh487 (http://dx.doi.org/10.1093/rheumatology/keh487). PMID 15561734 (http://www.ncbi.nlm.nih.gov/pubmed/15561734).
8. ^ Maddison P (2006). "Neuromyotonia". *Clinical neurophysiology : official journal of the International*